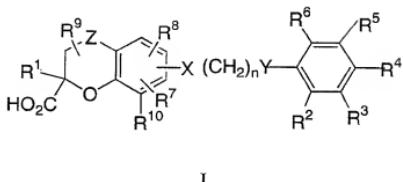


## WHAT IS CLAIMED IS:

## 1. A compound having the formula I:



or a pharmaceutically acceptable salt or prodrug thereof, wherein:

10

Z is selected from the group consisting of  $\text{CH}_2$  and  $\text{C}=\text{O}$ ;

15  $\text{R}^1$  is selected from the group consisting of H, -OH,  $\text{C}_1$ -7alkyl,  $\text{C}_2$ -7alkenyl,  $\text{C}_2$ -7alkynyl,  $-\text{OC}_1$ -3alkyl,  $-\text{OC}_2$ -3alkenyl,  $-\text{OC}_2$ -3alkynyl, F, Br, Cl, and Ar, wherein alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl and -Oalkynyl are linear or branched and are optionally substituted with (a) 1-7 halogen atoms, (b) 1-3 groups independently selected from (i)  $-\text{OC}_1$ -3alkyl, which is optionally substituted with 1-5 halogen atoms, and (ii) phenyl, which is optionally substituted with 1-3 groups independently selected from halogen,  $\text{C}_1$ -5alkyl and  $-\text{OC}_1$ -3alkyl, said  $\text{C}_1$ -5alkyl and  $-\text{OC}_1$ -3alkyl being linear or branched and optionally substituted with 1-5 halogens, or 20 (c) a mixture of (a) and (b); or alternatively,

$\text{R}^1$  is a group  $-\text{CR}^{11}\text{R}^{12}-$  which bridges between the carbon to which  $\text{R}^1$  is attached in Figure I and the adjacent carbon on the heterocyclic ring, yielding a cyclopropane ring;

25

$\text{R}^{11}$  and  $\text{R}^{12}$  are independently selected from the group consisting of hydrogen, halogen,  $\text{C}_1$ -5alkyl,  $\text{C}_2$ -5alkenyl,  $\text{C}_2$ -5alkynyl,  $-\text{OC}_1$ -3alkyl,  $-\text{OC}_2$ -3alkenyl,  $-\text{OC}_2$ -3alkynyl,  $-\text{CO}_2\text{H}$ ,  $-\text{CO}_2\text{C}_1$ -5alkyl,  $-\text{CO}_2\text{C}_2$ -5alkenyl,  $-\text{CO}_2\text{C}_2$ -5alkynyl, and phenyl, where alkyl, alkenyl, alkynyl, -Oalkyl, -Oalkenyl, -Oalkynyl - $\text{CO}_2$ alkyl, - $\text{CO}_2$ alkenyl, and - $\text{CO}_2$ alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogens, (b) 1-3 substituents independently

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selected from -OCH<sub>3</sub> and -OCF<sub>3</sub>, or (c) a mixture thereof, and phenyl is optionally substituted with 1-3 groups independently selected from halogen, C<sub>1</sub>-5alkyl, and -OC<sub>1</sub>-3alkyl, wherein C<sub>1</sub>-5alkyl and -OC<sub>1</sub>-3alkyl are linear or branched and are optionally substituted with 1-5 halogens;

5

Ar is selected from the group consisting of Aryl, Hetcyc, Hetaryl, and Benzoheterocycle, wherein Aryl, Hetcyc, Hetaryl, and Benzoheterocycle are in each instance optionally substituted with 1-5 substituents independently selected from (a) halogen, (b) C<sub>1</sub>-5alkyl, (c) C<sub>2</sub>-5alkenyl, (d) C<sub>2</sub>-5alkynyl, (e) -OC<sub>1</sub>-5alkyl, (f) -OC<sub>2</sub>-5alkenyl, (g) -OC<sub>2</sub>-5alkynyl, (h) -SO<sub>X</sub>C<sub>1</sub>-5alkyl, (i) -SO<sub>X</sub>NR<sup>a</sup>R<sup>b</sup>, (j) -SO<sub>X</sub>phenyl, (k) -C(O)C<sub>1</sub>-3alkyl, and (l) -C(O)NR<sup>a</sup>R<sup>b</sup>, wherein in each instance, each alkyl, alkenyl and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC<sub>1</sub>-3alkyl, which is linear or branched and is optionally substituted with 1-5 halogens, or (c) a mixture thereof, and wherein phenyl is optionally substituted with 1-3 substituents independently selected from halogen, C<sub>1</sub>-3alkyl, and C<sub>1</sub>-3alkoxy, wherein C<sub>1</sub>-3alkyl and C<sub>1</sub>-3alkoxy are linear or branched and are optionally substituted with 1-5 halogens, and wherein Hetcyc and Benzoheterocycle may each optionally have a C<sub>3</sub>-6-spiro-cycloalkyl substituent on the ring on a carbon atom that can have gem-disubstitution, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen;

25

x is selected from 0, 1 and 2;

Aryl is a carbocyclic 6-10 membered monocyclic or bicyclic aromatic ring system;

30

Hetcyc is a 5- or 6-membered saturated or partly saturated monocyclic heterocycle having 1-4 heteroatoms independently selected from N, S and O in the perimeter of the ring, wherein N may optionally be NR<sup>a</sup> and S may optionally be SO or SO<sub>2</sub>;

Hetaryl is a 5- or 6-membered heteroaromatic ring having 1-4 heteroatoms independently selected from O, S, and N in the perimeter of the ring, where N may optionally be NR<sup>a</sup>, and S may optionally be SO or SO<sub>2</sub>;

5           Benzoheterocycle comprises a 5 or 6-membered heterocyclic ring which may be saturated, partly unsaturated or aromatic, and a benzene ring, wherein said heterocyclic ring and said benzene ring are fused together, wherein said heterocyclic ring comprises 1-3 heteroatoms independently selected from O, S, and N in the perimeter of the ring, where N may optionally be NR<sup>a</sup>, and S may optionally be SO or SO<sub>2</sub>;

10           R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of H, C<sub>1</sub>-5alkyl, C<sub>2</sub>-5alkenyl, C<sub>2</sub>-5alkynyl, -C(O)C<sub>1</sub>-5alkyl, -C(O)C<sub>2</sub>-5alkenyl, -C(O)C<sub>2</sub>-5alkynyl, SO<sub>x</sub>C<sub>1</sub>-5alkyl, SO<sub>x</sub>phenyl, SO<sub>x</sub>NR<sup>d</sup>R<sup>e</sup>, -C(O)NR<sup>d</sup>R<sup>e</sup>, halogen, 15 and phenyl, wherein in all instances, alkyl, alkenyl, and alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from -OCH<sub>3</sub>, -OCF<sub>3</sub> and phenyl, or (c) a mixture thereof, wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C<sub>1</sub>-3alkyl, and C<sub>1</sub>-3alkoxy, said C<sub>1</sub>-3alkyl and 20 C<sub>1</sub>-3alkoxy being linear or branched and optionally substituted with 1-5 halogens;

25           R<sup>d</sup> and R<sup>e</sup> are independently selected from H, C<sub>1</sub>-5alkyl, C<sub>2</sub>-5alkenyl, C<sub>2</sub>-5alkynyl, and phenyl, wherein said alkyl, alkenyl, and alkynyl are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1-3 groups independently selected from -OCH<sub>3</sub>, -OCF<sub>3</sub> and phenyl, or (c) a mixture thereof, 30 wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C<sub>1</sub>-3alkyl, and C<sub>1</sub>-3alkoxy, said C<sub>1</sub>-3alkyl and C<sub>1</sub>-3alkoxy being linear or branched and optionally substituted with 1-5 halogens;

30           X and Y are independently selected from the group consisting of O, S, SO, SO<sub>2</sub>, NR<sup>a</sup> and CH<sub>2</sub>;

n is an integer from 1-6;

R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are independently selected from the group consisting of H, halogen, C<sub>1</sub>-7alkyl, C<sub>2</sub>-7alkenyl, C<sub>2</sub>-7alkynyl, -OH, -OC<sub>1</sub>-5alkyl, -OC<sub>2</sub>-5alkenyl, -OC<sub>2</sub>-5alkynyl, -C(O)C<sub>1</sub>-5alkyl, -C(O)C<sub>2</sub>-5alkenyl, -C(O)C<sub>2</sub>-5alkynyl, -C(O)OC<sub>1</sub>-5alkyl, -C(O)OC<sub>2</sub>-5alkenyl, -C(O)OC<sub>2</sub>-5alkynyl,

5 -OC(O)C<sub>1</sub>-5alkyl, -OC(O)C<sub>2</sub>-5alkenyl, -OC(O)C<sub>2</sub>-5alkynyl, Ar, -OAr, -C(O)Ar, -C(O)OAr, -OC(O)Ar, C<sub>3</sub>-8Cycloalkyl, -OC<sub>3</sub>-8Cycloalkyl, -SO<sub>X</sub>C<sub>1</sub>-5alkyl, -SO<sub>X</sub>NR<sup>a</sup>R<sup>b</sup>, -SO<sub>X</sub>Ar, and -C(O)NR<sup>a</sup>R<sup>b</sup>, wherein in each instance, each alkyl, alkenyl, and alkynyl is linear or branched and is optionally substituted with (a) 1-5 halogen atoms, (b) 1-2 groups independently selected from -OC<sub>1</sub>-3alkyl groups

10 which are linear or branched and are optionally substituted with 1-5 halogens, (c) 1 group Ar or C<sub>3</sub>-6Cycloalkyl, or (d) a mixture of more than one of (a), (b) and (c);

R<sup>4</sup> is selected from the group consisting of Benzoheterocycle, C<sub>3</sub>-8Cycloalkyl, Hetcyc, -OC<sub>3</sub>-8Cycloalkyl and R<sup>c</sup>, with the proviso that if R<sup>4</sup> is R<sup>c</sup>, then either (1) R<sup>1</sup> is not H, and no more than one of R<sub>2</sub>, R<sub>6</sub>, and R<sub>10</sub> is alkyl, or (2)

15 R<sup>2</sup> is Cl, Br or F, and R<sub>10</sub> is not alkyl;

wherein Benzoheterocycle, C<sub>3</sub>-8Cycloalkyl, Hetcyc and -OC<sub>3</sub>-8Cycloalkyl are each optionally substituted with 1-3 groups independently selected from halogen, C<sub>1</sub>-5alkyl, C<sub>2</sub>-5alkenyl, C<sub>2</sub>-5alkynyl, -OC<sub>1</sub>-5alkyl, -OC<sub>2</sub>-5alkenyl, -OC<sub>2</sub>-5alkynyl, C<sub>3</sub>-8Cycloalkyl, -SO<sub>X</sub>C<sub>1</sub>-5alkyl, -SO<sub>X</sub>NR<sup>a</sup>R<sup>b</sup>, -SO<sub>X</sub>phenyl, C(O)C<sub>1</sub>-3alkyl and -C(O)NR<sup>a</sup>R<sup>b</sup>, wherein in all instances, said C<sub>1</sub>-5alkyl, C<sub>2</sub>-5alkenyl, and C<sub>2</sub>-5alkynyl groups are linear or branched and are optionally substituted with 1-3 halogens, and wherein Hetcyc, -OC<sub>3</sub>-8Cycloalkyl and C<sub>3</sub>-8Cycloalkyl may optionally have a C<sub>3</sub>-6-spiro-cycloalkyl substituent on the ring where gem-disubstitution of a ring carbon is possible, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen;

25 wherein R<sup>c</sup> is selected from the group consisting of halogen, -OH, -OSO<sub>2</sub>C<sub>1</sub>-8alkyl, -OSO<sub>2</sub>C<sub>3</sub>-8Cycloalkyl, -OSO<sub>2</sub>Ar, C<sub>1</sub>-8alkyl, C<sub>2</sub>-8alkenyl, C<sub>2</sub>-8alkynyl, -OC<sub>1</sub>-8alkyl, -OC<sub>2</sub>-8alkenyl, -OC<sub>2</sub>-8alkynyl, and Aryl, wherein said

30 -OSO<sub>2</sub>C<sub>1</sub>-8alkyl, C<sub>1</sub>-8alkyl, C<sub>2</sub>-8alkenyl, C<sub>2</sub>-8alkynyl, -OC<sub>1</sub>-8alkyl, -OC<sub>2</sub>-8alkenyl, and -OC<sub>2</sub>-8alkynyl are linear or branched, and are optionally substituted with (a) 1-5 halogens, (b) 1-2 groups independently selected from -OC<sub>1</sub>-3alkyl, which are linear or branched and which are optionally substituted with 1-5 halogens, (c) 1 group selected from Aryl and C<sub>3</sub>-8Cycloalkyl, or (d) a mixture of one or more of (a), (b)

and (c), and Aryl and C<sub>3</sub>-8Cycloalkyl are each optionally substituted as defined under Ar for Aryl and R<sup>4</sup> for C<sub>3</sub>-8Cycloalkyl;

or alternatively R<sup>4</sup> and the adjacent substituent R<sup>3</sup> or R<sup>5</sup> may be  
5 connected to form a 5- or 6-membered heterocyclic ring that may be saturated, partly  
unsaturated or aromatic fused to the benzene ring, wherein the 5- or 6-membered  
fused ring comprises 1-3 heteroatoms independently selected from O, S, and N, where  
N may optionally be NR<sup>a</sup> and S may optionally be SO or SO<sub>2</sub>, said fused ring  
optionally also comprising 1-2 C=O groups in the perimeter of the ring, wherein  
10 said 5- or 6-membered heterocyclic fused ring is optionally substituted with 1-2  
groups independently selected from R<sup>3</sup>.

2. A compound having formula I as recited in Claim 1, wherein X and  
Y are each O or S.

15 3. A compound having formula I as recited in Claim 1, wherein X and  
Y are O.

20 4. A compound having formula I as recited in Claim 1, wherein Z is  
CH<sub>2</sub>.

5. A compound having formula I as recited in Claim 1, wherein Z is  
C=O.

25 6. A compound having formula I as recited in Claim 1, wherein n is 3  
or 4.

30 7. A compound having formula I as recited in Claim 1, wherein R<sup>1</sup> is  
selected from the group consisting of Cl, Br, F and C<sub>1</sub>-4 alkyl, wherein said C<sub>1</sub>-4alkyl  
is linear or branched and is optionally substituted with 1-3 halogens independently  
selected from F and Cl, 1 phenyl which is optionally substituted with 1-3 halogens, or  
a mixture thereof.

8. A compound having formula I as recited in Claim 1, wherein R<sup>2</sup> is selected from the group consisting of Cl, Br, F and C<sub>1-4</sub>alkyl, wherein said C<sub>1-4</sub>alkyl is optionally substituted with 1-3 halogens.

5 9. A compound having formula I as recited in Claim 1, wherein the group -X- is attached to the benzopyran ring at the 6-position of the benzopyran ring.

10 10. A compound having formula I as recited in Claim 1, wherein the group -X- is attached to the benzopyran ring at the 7-position of the benzopyran ring.

11 11. A compound having formula I as recited in Claim 1, wherein R<sup>1</sup> is selected from a group consisting of C<sub>1-4</sub>alkyl, Cl and F, wherein alkyl is linear or branched and is optionally substituted with 1-5 F.

12 12. A compound as recited in claim 1, wherein Ar is phenyl, which is optionally substituted with 1-4 groups independently selected from Cl, F, C<sub>1-5</sub>alkyl, -OCH<sub>3</sub>, -OCF<sub>3</sub>, -SO<sub>X</sub>C<sub>1-5</sub>alkyl, -SO<sub>X</sub>NR<sub>a</sub>R<sub>b</sub>, -SO<sub>X</sub>phenyl, -C(O)C<sub>1-3</sub>alkyl, and -C(O)NR<sup>a</sup>R<sup>b</sup>, wherein phenyl of -SO<sub>X</sub>phenyl is optionally substituted with 1-3 substituents independently selected from halogen, CH<sub>3</sub>, CF<sub>3</sub>, -OCF<sub>3</sub>, and -OCH<sub>3</sub>, and wherein alkyl in all occurrences is linear or branched and is optionally substituted with 1-5 halogens.

25 13. A compound as recited in claim 1, wherein R<sup>1</sup> and R<sup>2</sup> are each independently selected from a group consisting of C<sub>1-4</sub>alkyl, Cl and F; n is 2-4; X and Y are O; Z is CH<sub>2</sub>; R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup> and R<sup>10</sup> are independently selected from H, Cl, F, CH<sub>3</sub> and CF<sub>3</sub>; and in all occurrences, alkyl is linear or branched and is optionally substituted with 1-5 F.

30 14. A compound having formula I as recited in any one of Claims 1-13, wherein R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> are H; R<sup>2</sup> is Cl or F; and R<sup>1</sup> is C<sub>1-4</sub>alkyl, Cl or F, where C<sub>1-4</sub>alkyl is linear or branched and is optionally substituted with 1-5 F.

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15. A compound having formula I as recited in Claim 1, wherein R<sup>3</sup>, R<sup>5</sup> and R<sup>6</sup> are H.

5 16. A compound as recited in Claim 1, wherein R<sup>a</sup> and R<sup>b</sup> are independently selected from the group consisting of H, C<sub>1-5</sub>alkyl, -C(O)C<sub>1-5</sub>alkyl, S(O)<sub>x</sub>C<sub>1-5</sub>alkyl, S(O)xphenyl, and phenyl, wherein alkyl in all occurrences is linear or branched and is optionally substituted with 1-5 halogen atoms, and wherein phenyl in all occurrences is optionally substituted with 1-3 substituents independently selected from halogen, C<sub>1-3</sub>alkyl, and C<sub>1-3</sub>alkoxy, wherein C<sub>1-3</sub>alkyl and C<sub>1-3</sub>alkoxy are linear or branched and are optionally substituted with 1-5 halogens.

10 17. A compound as recited in Claim 1, wherein R<sup>1</sup> is not H or -CR<sup>11</sup>R<sup>12</sup>, and no more than one of R<sup>2</sup>, R<sup>6</sup>, and R<sup>10</sup> is alkyl.

15 18. A compound as recited in Claim 1, wherein R<sup>2</sup> is Cl, Br or F, and R<sup>10</sup> is not alkyl.

19. A compound having Formula I as recited in Claim 1, wherein 20 R<sup>4</sup> is joined to R<sup>3</sup> or to R<sup>5</sup> to yield a benzoheterocycle which comprises a 5 or 6-membered heterocyclic ring which may be saturated, partly unsaturated or aromatic fused to the benzene ring, wherein said benzoheterocycle is selected from the group consisting of benzoxazole, benzisoxazole, benzofuran, indole, benzothiophene, benzthiazole, benzodiazene, quinazoline, benzoxazine, benzisoxazine, benzimidazole, 25 and benzpyrazole, wherein said benzoheterocycle is optionally substituted on the heterocyclic ring with 1-2 groups independently selected from halogen, phenyl, C<sub>1-4</sub>alkyl, and -OC<sub>1-4</sub>alkyl, wherein C<sub>1-4</sub>alkyl and -OC<sub>1-4</sub>alkyl are linear or branched and are optionally substituted with 1-5 halogens, and said phenyl is optionally substituted with 1-5 substituents independently selected from halogen, C<sub>1-3</sub>alkyl and C<sub>1-3</sub>alkoxy groups, wherein the C<sub>1-3</sub>alkyl and C<sub>1-3</sub>alkoxy groups are 30 linear or branched and are optionally substituted with 1-5 halogens.

20. A compound having formula I as recited in Claim 19, wherein 35 R<sup>4</sup> and R<sup>3</sup> or R<sup>5</sup> are joined together to form a benzisoxazole ring, which is optionally substituted on the isoxazole ring with 1 group selected from C<sub>1-4</sub>alkyl and phenyl,

wherein C<sub>1</sub>-4alkyl is linear or branched and is optionally substituted with (a) 1-3 halogens, (b) 1 phenyl, or (c) a mixture of (a) and (b); and phenyl in all occurrences is optionally substituted with 1-3 groups independently selected from halogen, C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl, wherein said C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl are linear or  
5 branched and are optionally substituted with 1-3 halogens.

21. A compound having Formula I as recited in Claim 1, wherein  
R<sup>4</sup> is selected from the group consisting of C<sub>3</sub>-8Cycloalkyl and Hetcyc, each of which  
10 is optionally substituted with 1-4 substituents independently selected from halogen, phenyl, C<sub>1</sub>-5alkyl, and -OC<sub>1</sub>-5alkyl, wherein C<sub>1</sub>-5alkyl and -OC<sub>1</sub>-5alkyl are linear or branched and are optionally substituted with 1-5 halogens, and phenyl is optionally substituted with 1-5 substituents independently selected from halogen, C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl, wherein C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl are linear or branched and are  
15 optionally substituted with 1-5 halogens, and  
wherein two substituents on the same carbon of said C<sub>3</sub>-8Cycloalkyl and Hetcyc may optionally join together to form a C<sub>3</sub>-6-spiro-cycloalkyl group, wherein the spiro-cycloalkyl group is optionally substituted with 1-2 groups independently selected from methyl, trifluoromethyl, methoxy, trifluoromethoxy and halogen.  
20

22. A compound having Formula I as recited in Claim 21, wherein  
R<sup>4</sup> is Hetcyc or C<sub>3</sub>-6Cycloalkyl, wherein Hetcyc is a saturated heterocyclic compound having 1-2 heteroatoms in the perimeter of the ring and is otherwise as defined in Claim 1, and C<sub>3</sub>-6Cycloalkyl is a saturated 3-6-membered cycloalkyl, wherein Hetcyc and C<sub>3</sub>-6Cycloalkyl optionally have 1-2 substituents independently selected from halogen, C<sub>1</sub>-3alkyl and C<sub>2</sub>-3alkenyl, wherein said C<sub>1</sub>-3alkyl and C<sub>2</sub>-3alkenyl are linear or branched and are optionally substituted with 1-3 halogens, or alternatively two substituents may be joined on one carbon atom of the ring to form  
30 a spiro-cycloalkyl group having 3-6 carbons.

23. A compound having formula I as recited in Claim 22, wherein  
R<sup>4</sup> is selected from piperidine, 1,4-dioxane, tetrahydropyran, piperazine, morpholine,

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cyclohexane, cyclopentane, cyclobutane and cyclopropane, wherein R<sup>4</sup> is optionally substituted as defined in Claim 22.

24. A compound having formula I as recited in Claim 23, wherein

5 R<sup>4</sup> is R<sup>c</sup> and is selected from the group consisting of halogen, C<sub>1</sub>-8alkyl, C<sub>2</sub>-8alkenyl, C<sub>2</sub>-8alkynyl, -OC<sub>1</sub>-8alkyl, -OC<sub>2</sub>-8alkenyl, -OC<sub>2</sub>-8alkynyl, and Aryl, wherein C<sub>1</sub>-8alkyl, C<sub>2</sub>-8alkenyl, C<sub>2</sub>-8alkynyl, -OC<sub>1</sub>-8alkyl, -OC<sub>2</sub>-8alkenyl, and -OC<sub>2</sub>-8alkynyl are linear or branched, and are optionally substituted with (a) 1-5 halogens, (b) 1-2 groups independently selected from -OC<sub>1</sub>-3alkyl, which are linear

10 or branched and which are optionally substituted with 1-5 halogens, (c) 1 group Aryl or C<sub>3</sub>-8Cycloalkyl, or (d) a mixture of more than one of (a), (b) and (c), wherein Aryl and C<sub>3</sub>-8Cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl, said C<sub>1</sub>-3alkyl and -OC<sub>1</sub>-3alkyl being linear or branched and optionally substituted with 1-5 halogens, phenyl or

15 C<sub>3</sub>-6Cycloalkyl.

25. A compound having formula I as recited in Claim 24, wherein

R<sup>4</sup> is selected from the group consisting of C<sub>1</sub>-4alkyl and -OC<sub>1</sub>-4alkyl, wherein said C<sub>1</sub>-4alkyl and -OC<sub>1</sub>-4alkyl are linear or branched and are optionally substituted with

20 one C<sub>3</sub>-6Cycloalkyl group, 1-5 halogens independently selected from Cl and F, or a mixture of both.

26. A compound having formula I as recited in Claim 24, wherein

Aryl is phenyl; R<sup>1</sup> is selected from a group consisting of C<sub>1</sub>-4alkyl, Cl and F, wherein

25 alkyl is linear or branched and is optionally substituted with 1-5 F; R<sup>2</sup> is selected from Cl and F; and R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> are independently selected from H, CH<sub>3</sub>, CF<sub>3</sub>, Cl and F.

27. A compound having formula I as recited in any one of Claims

30 1-26, wherein R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, and R<sup>10</sup> are H; R<sup>1</sup> is C<sub>1</sub>-4alkyl, Cl or F; and R<sup>2</sup> is Cl or F.

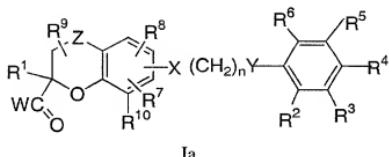
28. A compound having formula I as recited in Claim 1, wherein

R<sup>1</sup> is selected from linear or branched C<sub>1</sub>-4 alkyl, Cl and F; R<sup>2</sup> is Cl or F; R<sup>3</sup>, R<sup>5</sup>,

R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, R<sub>9</sub> and R<sub>10</sub> are each H; Z is CH<sub>2</sub>; X and Y are O or S; and R<sup>4</sup> is selected from halogen, phenyl, C<sub>1</sub>-8alkyl, -OC<sub>1</sub>-8alkyl, C<sub>3</sub>-6Cycloalkyl, and tetrahydropyran, wherein said C<sub>1</sub>-8alkyl and -OC<sub>1</sub>-8alkyl groups are linear or branched and are optionally substituted with (a) 1-5 halogen atoms, (b) 1 group selected from phenyl, C<sub>3</sub>-6Cycloalkyl, and linear or branched -OC<sub>1</sub>-3alkyl optionally substituted with 1-5 halogens, or (c) a mixture of (a) and (b), and wherein said phenyl, C<sub>3</sub>-6Cycloalkyl and tetrahydropyran groups are optionally substituted with 1-2 groups independently selected from halogen, -OCH<sub>3</sub>, -CH<sub>3</sub>, -OCF<sub>3</sub>, and -CF<sub>3</sub>.

10

29. A compound having formula Ia:



15

or a pharmaceutically acceptable salt or metabolite thereof, wherein W is a group that is easily removed under physiological conditions during or after administration to a mammalian patient to yield a carboxylic acid in which W is OH, or the carboxylate anion thereof, or a pharmaceutically acceptable salt thereof, and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>,

20 R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, Ar, X, Y, Z, R<sup>a</sup>, R<sup>b</sup>, R<sup>d</sup>, R<sup>e</sup>, x and n are as defined in Claim 1.

25

30. A compound as recited in Claim 29, wherein W is selected from the group consisting of -OR<sup>13</sup>, -OCH<sub>2</sub>OR<sup>13</sup>, -OCH(CH<sub>3</sub>)OR<sup>13</sup>, -OCH<sub>2</sub>OC(O)R<sup>13</sup>, -OCH(CH<sub>3</sub>)OC(O)R<sup>13</sup>, -OCH<sub>2</sub>OC(O)OR<sup>13</sup>, -OCH(CH<sub>3</sub>)OC(O)OR<sup>13</sup>, and -NR<sup>14</sup>R<sup>14</sup>, wherein each R<sup>13</sup> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with one or two groups independently selected from -CO<sub>2</sub>H, -CONH<sub>2</sub>, NH<sub>2</sub>, -OH, -OAc, NHAc and phenyl; and

wherein each R<sup>14</sup> is independently selected from H and R<sup>13</sup>.

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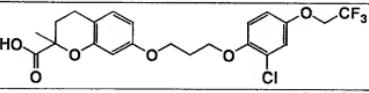
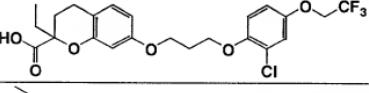
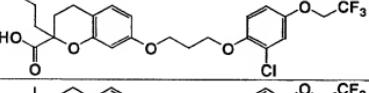
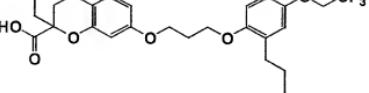
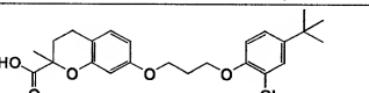
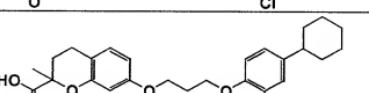
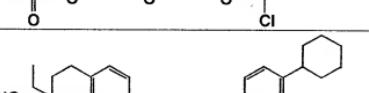
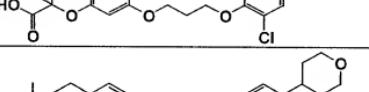
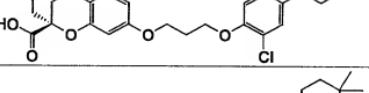
31. A compound as recited in any one of Claims 1-30, wherein the stereochemistry at the 2-position of the benzopyranyl ring is R.

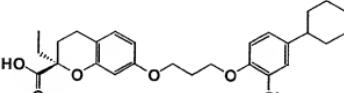
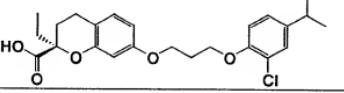
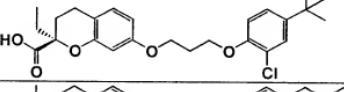
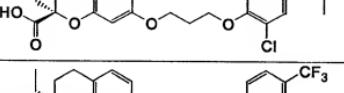
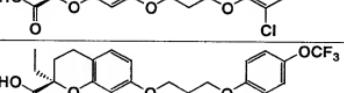
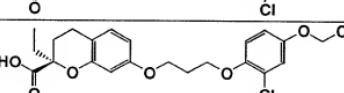
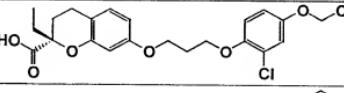
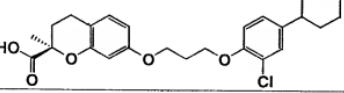
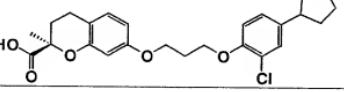
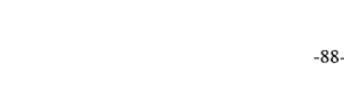
5 32. A compound as recited in any one of Claims 1-30, wherein the stereochemistry at the 2-position of the benzopyranyl ring is S.

33. A compound represented by any of the structures of Examples 1- 29, shown below, or a pharmaceutically acceptable salt or prodrug thereof:

10

	Example 1
	Example 2
	Example 3
	Example 4
	Example 5

	Example 6
	Example 7
	Example 8
	Example 9
	Example 10
	Example 11
	Example 12
	Example 13
	Example 14

	Example 15
	Example 16
	Example 17
	Example 18
	Example 19
	Example 20
	Example 21
	Example 22
	Example 23
	Example 24

	Example 25
	Example 26
	Example 27
	Example 28
	Example 29

34. A compound according to Claim 1, selected from the list of compounds below, or a pharmaceutically acceptable salt or prodrug thereof:

5

Example 1: 7-(3-(3-Trifluoromethyl-7-propyl-6-benz-[4,5]-isoxazoloxyl)propoxy)-2-ethylchromane-2-carboxylic acid;

10 Example 2: 7-(3-(3-(2,2-Dimethylpropyl)-7-propyl-6-benz-[4,5]-isoxazoloxyl)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 3: 7-(3-(3-Phenyl-7-propyl-6-benz-[4,5]-isoxazoloxyl)propoxy)-2-methylchromane-2-carboxylic acid;

15 Example 4: 7-(3-(4-(1,2-Benzisoxazol-3-yl)-2-propylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 5: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-chromane-2-carboxylic acid;

5 Example 6: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 7: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

10 Example 8: 7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-propylchromane-2-carboxylic acid;

Example 9: 7-(3-(2-Propyl-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

15 Example 10: 7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

20 Example 11: 7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 12: 7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

25 Example 13: (2R)-7-(3-(2-Chloro-4-(4-tetrahydropyranyl)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 14: (2R)-7-(3-(2-Chloro-4-(4,4-dimethylcyclohexyl)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

30

Example 15: (2R)-7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 16: (2R)-7-(3-(2-Chloro-4-isopropylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

5 Example 17: (2R)-7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 18: (2R)-7-(3-(2-Chloro-4-isobutylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

10 Example 19: (2R)-7-(3-(2-Chloro-4-trifluoromethylphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 20: (2R)-7-(3-(2-Chloro-4-trifluoromethoxyphenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

15 Example 21: (2R)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

Example 22: (2S)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid;

20 Example 23: (2R)-7-(3-(2-Chloro-4-cyclohexylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 24: (2R)-7-(3-(2-Chloro-4-cyclopentylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

25 Example 25: (2R)-7-(3-(2-Chloro-4-tert-butylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 26: (2R)-7-(3-(2-Chloro-4-isobutylphenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 27: (2R)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid;

Example 28: (2R)-7-(3-(2-Chloro-4-(4-tetrahydropyranyl)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid; and

5      Example 29: (2S)-7-(3-(2-Chloro-4-(2,2,2-trifluoroethoxy)phenoxy)propoxy)-2-methylchromane-2-carboxylic acid.

10      35.     A pharmaceutical composition comprising a compound as identified in any of Claims 1-34 and a pharmaceutically acceptable carrier.

15      36.     A method for treating, controlling, or preventing non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

15      37.     A method for treating, controlling or preventing hyperglycemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

20      38.     A method for treating, controlling or preventing lipid disorders, hyperlipidemia, or low HDL in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

25      39.     A method for treating, controlling or preventing obesity in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

30      40.     A method for treating, controlling or preventing hypercholesterolemia in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

35      41.     A method for treating, controlling or preventing hypertriglyceridemia in a mammalian patient in need of such treatment which

comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

42. A method for treating, controlling or preventing dyslipidemia 5 and/or low HDL cholesterol in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

43. A method for treating, controlling or preventing atherosclerosis 10 in a mammalian patient in need of such treatment which comprises administering to said patient a therapeutically effective amount of a compound of Claim 1.

44. A method for treating, controlling or preventing cachexia in a mammalian patient in need of such treatment which comprises administering to said 15 patient a therapeutically effective amount of a compound of Claim 1.

45. A method of treating, controlling or preventing one or more diseases, disorders, or conditions selected from the group consisting of (1) non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) impaired glucose tolerance, (4) insulin resistance, (5) obesity, (6) lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) acne vulgaris, (30) skin diseases modulated by PPAR, (31) high blood pressure, (32) Syndrome X, (33) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, said method comprising the administration of an effective amount of a compound of Claim 1.

46. A method of treating, controlling or preventing one or more diseases, disorders, or conditions selected from the group consisting of (1) diabetes mellitus, and especially non-insulin dependent diabetes mellitus (NIDDM), (2) hyperglycemia, (3) impaired glucose tolerance, (4) insulin resistance, (5) obesity, (6) 5 lipid disorders, (7) dyslipidemia, (8) hyperlipidemia, (9) hypertriglyceridemia, (10) hypercholesterolemia, (11) low HDL levels, (12) high LDL levels, (13) atherosclerosis and its sequelae, (14) vascular restenosis, (15) irritable bowel syndrome, (16) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (17) other inflammatory conditions, (18) pancreatitis, (19) abdominal 10 obesity, (20) neurodegenerative disease, (21) retinopathy, (22) neoplastic conditions, (23) adipose cell tumors, (24) adipose cell carcinomas, such as liposarcoma, (25) prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, (26) angiogenesis, (27) Alzheimer's disease, (28) psoriasis, (29) acne vulgaris, (30) skin diseases modulated by PPAR, (31) high blood pressure, (32) Syndrome X, 15 (33) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component, said method comprising the administration of an effective amount of a compound of Claim 1, and an effective amount of one or more other compounds selected from the group consisting of:

- (a) insulin sensitizers including (i) PPAR $\gamma$  agonists such as the 20 glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV inhibitors;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d)  $\alpha$ -glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as (i) HMG-CoA reductase 25 inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR $\alpha$  agonists such as fibric acid derivatives (clofibrate, fenofibrate and bezafibrate) or gemfibrozil, (v) PPAR $\alpha/\gamma$  dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example

ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;

(f) PPAR $\delta$  agonists such as those disclosed in WO97/28149;

(g) antidiobesity compounds (anorectics) such as fenfluramine,

5 dexfenfluramine, phentermine, sibutramine, mazindol, orlistat, lipase inhibitors, neuropeptide Y5 inhibitors, and  $\beta_3$  adrenergic receptor agonists;

(h) an ileal bile acid transporter inhibitor; and

(i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclo-

10 oxygenase 2 selective inhibitors.

47. A method for the treatment, control, or prevention of one or more conditions selected from hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which

15 method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of Claim 1 and a therapeutically effective amount of an HMG-CoA reductase inhibitor.

48. The method as recited in Claim 47, wherein the HMG-CoA 20 reductase inhibitor is a statin.

49. The method as recited in Claim 48, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

25 50. A method for the treatment, control, or prevention of one or more conditions selected from inflammatory conditions, inflammatory bowel disease, Crohn's disease, and ulcerative colitis, which method comprises administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound according to Claim 1.

30 51. A method for treating, preventing or controlling atherosclerosis in a mammalian patient in need of such treatment comprising the administration to said patient of an effective amount of a compound of Claim 1 and an effective amount 35 of an HMG-CoA reductase inhibitor.

52. The method as recited in Claim 51, wherein the HMG-CoA reductase inhibitor is a statin.

5 53. The method as recited in Claim 52, wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

10 54. A pharmaceutical composition for the treatment, prevention or control of atherosclerosis, comprising: (1) a compound according to Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

15 55. A pharmaceutical composition comprising (1) a compound according to Claim 1, (2) one or more compounds selected from the group consisting of :

20 (a) insulin sensitizers including (i) PPAR $\gamma$  agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin and phenformin; (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, and (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;

25 (b) insulin or insulin mimetics;

(c) sulfonylureas such as tolbutamide and glipizide, or related materials;

30 (d)  $\alpha$ -glucosidase inhibitors (such as acarbose);

(e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR $\alpha$  agonists such as fibrac acid derivatives (clofibrate, fenofibrate and bezafibrate) or gemfibrozil, (v) PPAR $\alpha/\gamma$  dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as for example ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and (viii) anti-oxidants, such as probucol;

35 (f) PPAR $\delta$  agonists such as those disclosed in WO97/28149;

(g) antiobesity compounds (anorectics) such as fenfluramine, dexfenfluramine, phentermine, sibutramine, mazindol, orlistat, lipase inhibitors, neuropeptide Y5 inhibitors, and  $\beta_3$  adrenergic receptor agonists;

5 (h) an ileal bile acid transporter inhibitor; and

(i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclooxygenase 2 selective inhibitors; and

(3) a pharmaceutically acceptable carrier.

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